## REMARKS

Claims 1, 3-9, 21, 23-29, 37, 39-40 and 45-46 are now pending for prosecution in this case, Claims 17, 19-20 and 41-44 have been withdrawn from consideration as being drawn to a non-elected invention and Claims 2, 10-15, 22, 30-36 and 38 have been cancelled by amendment herewith.

***Preliminary Observations and Objections***

The Examiner has noted that Claims 1-4, 8-16, 18 and 21-39 are allegedly "significantly different", from the original claims of U.S.S.N. 09/380,142, and as a result, are allegedly not entitled to the filing date of this application.

Continuing, the Examiner notes that while the '142 priority application teaches that IL-17 contributes to the loss of articular cartilage in arthritic joints and that inhibiting it limits inflammation and cartilage destruction and would be useful to treat inflammatory conditions and cartilage defects such as arthritis. However, the Examiner further alleges that the '142 priority application does not teach specifically the entire genus of cartilage disorders (*e.g.*, Claims 1-3, 8-9, 13-16, 18 and 37-38), anti-IL-17 antibody (*e.g.*, Claims 2, 38), degenerative cartilagenous disorders (Claims 1-4, 39), injury-induced cartilagenous disorders (Claims 10-12), a standard surgical technique, pharmaceutical compositions of IL-17 antagonists (Claim 13) or combination therapy of IL-17 antagonist and at least one cartilage agent (Claims 15, 16 and 18) and a method of preventing cartilage damage (Claims 21-36).

In response, Applicants respectfully disagree that the '142 priority application does not specifically teach the use of: (1) the anti-IL17 antibodies and the use of IL-17 antagonists for the treatment of degenerative cartilagenous disorders. The preparation and use of IL-17 antagonists is described at page 62 through page 66, line 17. The specific use of IL-17 antibodies is also described at page 62, lines 23-25. Moreover, antibodies are broadly included as inclusive of antagonists at page 22, line 29 through page 23, line 7. Continuing, example 16, page 88, line 30 through page 91, line 5 of the '142 priority application describe the effects of IL-17 on inflammation and articular cartilage destruction, specifically degenerative cartilagenous disorders such as arthritis. (See page 90, lines 14-20).

Mention of the other objectionable subject matter areas recited above as objectionable has been removed from the claims, without prejudice or disclaimer for future claims directed at the deleted subject matter.

Finally, the Examiner objects to Claims 1-16, 18 and 21-40 for encompassing non-elected subject matter, namely an antagonist to LIF.

In response, Applicants have amended the claims at issue by canceling mention of LIF.

***The Rejection under 35 U.S.C. § 112, First Paragraph***

Claims 1-5, 7-16, 18 and 21-40 stand rejected under 35 U.S.C. § 112, First Paragraph, as being enabling for a method of treating rheumatoid or osteoarthritis, but allegedly not being enabling for a method of treating "any or all cartilagenous disorders, degenerative cartilagenous disorders or arthritis, or to a method of preventing these disorders, including RA and OA."

The Examiner acknowledges IL-17 has a proinflammatory effect, induces NO (nitric oxide) production in chondrocytes and is expressed in arthritic cartilage. Moreover, the Examiner acknowledges that the specification demonstrates the deleterious effects of IL-17 on explant or cell culture on cartilage matrix turnover and metabolism and provides a working example of treating rheumatoid arthritis *in vivo*, showing that anti-IL-17 antibodies exhibit decreased disease progression.

However, the Examiner argues that the specification does not provide evidence that antagonism of IL-17 is effective for the treatment of all cartilagenous disorders or that such a method can prevent damage caused by cartilagenous disorders in that not all cartilagenous disorders are inflammatory, including those resulting from injury.

In response, Applicants have amended the claimed method to provide for a method of inhibiting IL-17 mediated inflammatory cartilagenous disorders, thereby rendering the application of the rejection moot. Moreover, Applicants have adopted the Examiner's suggested claim language directed to replacing "preventing" with "reducing further damage" in order to obviate the rejection to remaining Claims 21 and 23-29 (Claim 22 having been cancelled).

Applicants respectfully request reconsideration and withdrawal of the rejection of Claims

1, 3-5, 7-9 and 21, 23-29, 37, 39-40 under 35 U.S.C. § 112, First Paragraph (Claims 2, 10-16, 22 and 30-36 having been cancelled).

***The Rejection under 35 U.S.C. § 112, Second Paragraph***

Claims 1-16, 18 and 21-40 stand rejected under 35 U.S.C. § 112, Second Paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter of the invention.

Specifically, the Examiner has alleged the following:

(1) Claims 1, 8, 15, 18, 21, 28, 35 and 37 are unclear for using the term "effective amount";

(2) Claim 15 is unclear what is a "cartilage agent";

(3) Claim 18 is unclear for using the language "and variants thereof";

(4) Claim 21 is unclear what is intended by "preventing cartilage damage";

(5) Claims 14 and 34 are unclear for using language "standard surgical technique";

(6) Claim 16 is unclear what is a "catabolism antagonist" is;

(7) Claims 22 and 38 are indefinite for using the conjunction "and" in the context of "wherein the IL-17 and LIF are anti-IL-17 and anti-LIF antibodies;

(8) Claim 33 is vague because it is unclear how "the effective amount of" can "further comprise a carrier or . . .".

In response, Applicants respectfully submit the following:

(1) "Effective amount" is defined at page 21, lines 27-31. In particular, an "effective amount" is "at least the minimum concentration of IL-17 . . . which causes, induce or results in either a detectable improvement of repair in damaged cartilage or provides a measurable degree of protection from the continued or induced cartilage destruction in an isolated sample of cartilage matrix (*e.g.*, retention of proteoglycans in the matrix, inhibition of proteoglycan release from the matrix, stimulation of proteoglycan synthesis);"

(2)-(3) Claims 15 and 18 have been cancelled, thereby rendering the rejection moot;

(4) "Preventing cartilage damage" has been replaced with the Examiner's suggested language in Claim 21, thereby obviating the rejection;

(5)-(6) Claims 14, 16 and 34 have been cancelled, thereby rendering the rejection moot;

(7) Claims 22 and 38 have been amended to cancel the text referring to anti-LIF antibodies, thereby rendering the rejection moot;

(8) "Therapeutically effective amount" is defined at page 21, lines 31-36. In particular a "therapeutically effective amount" is "at least the minimum concentration (amount) or IL-17 . . . antagonist administered to a mammal which would be effective in at least attenuating a pathological symptom (*e.g.*, causing, inducing or resulting in a measurable improvement or repair in damaged articular cartilage or causing, inducing or resulting in a measurable protection from the continued or initial cartilage destruction, improvement in range or motion, reduction in pain, etc.) which occurs as a result of injury or a cartilagenous disorder."

Applicants respectfully request reconsideration and withdrawal of the rejection of 1, 3-9, 21, 23-29, 37 and 39-40 stand rejected under 35 U.S.C. § 112, Second Paragraph (Claims 2, 10-18, 22, 30-36 and 38 having been cancelled).

***The First Rejection under 35 U.S.C. § 102***

Claims 1-9, 13, 14, 21-26, 28-29, 33, 34 and 37-40 stand rejected under 35 U.S.C. § 102(a), as allegedly being anticipated by Troutt (WO 98/23284).

In particular, the Examiner argues that Troutt *et al.* discloses a method of treating OA and RA comprising administering soluble IL-17R in conjunction with other immunoregulatory molecules, such as IL-1Ra (page 2, para. 4; page 16, para. 4). Allegedly, Claims 1-9 (method of treating OA and RA), Claims 13-14 (method of treating IL-17 antagonist with a carrier, and in combination with standard surgical technique), Claims 14, 21-26, 28, 29, 33 and 34 (as an inherent property), Claims 37-40 (OA and RA patients are mammals) are anticipated.

In response, Applicants have amended the claims at issue to specify a method of using anti-IL-17. Troutt *et al.*, does not disclose, discuss or infer that anti-IL-17 antibody may be used to treat IL-17-mediated inflammatory disorders. As a result, the claimed subject matter is not "patented or described in a printed publication" within the meaning of 35 U.S.C. § 102(a).

Applicants respectfully request reconsideration and withdrawal of the rejection of Claims 1-9, 21-26, 28-29 and 37-40 stand rejected under 35 U.S.C. § 102(a) (Claims 13-14 and 33-34 having been cancelled).

***The Second Rejection under 35 U.S.C. § 102***

Claims 1-4, 8-9, 13-14, 21-26, 28, 29, 33-34 and 37-39 stand rejected under 35 U.S.C. §102, as allegedly being anticipated by Shigeru *et al.* (JP 2001186046).

In particular, the Examiner alleges that Shigeru *et al.* discloses that levels of IL-17 in the synovial fluids of RA patients are significantly higher and that anti-IL-17 antibody is able to inhibit IL-17-induced osteoclastogenesis, and is antirheumatic and antiarthritic. Furthermore, Shigeru *et al.* is alleged to disclose a method of treating bone joint destruction using anti-IL-17, an IL-17 antagonist, thereby allegedly anticipating Claims 1-4, 8-9, 13, 14 and 37-39. The Examiner further argues that Claims 21-26, 28-29, 33 and 34 are anticipated because the "preventing features" would be an inherent property of the IL-17 antibody. Lastly, Claim 13 is alleged to be anticipated because the anti-IL-17 antibodies of Shigeru *et al.* are dissolved in saline or buffer.

In response, Applicants respectfully submit the effective date of Shigeru *et al.* is July 4, 2000, while the effective priority date of the present invention, as presently claimed, is at least May 14, 1999. Thus, the claimed subject matter was not "patented or described in a printed publication" within the meaning of 35 U.S.C. § 102(a). Applicants respectfully request reconsideration and withdrawal of the rejection of Claims 1-4, 8-9, 21-26, 28, 29 and 37-39 under 35 U.S.C. § 102 (Claims 13-14, 33-34 having been cancelled).

***The First Rejection under 35 U.S.C. § 103***

Claims 1-9, 13-14, 21-26, 28-29, 33-34 and 37-40 stand rejected under 35 U.S.C. § 103, as allegedly being unpatentable over Chabaud *et al.*, *J. Immunol.* 161: 409-414 (1998) in view of Carroll *et al.*, *Inflammation Res.* 47: 1-7 (1998). The Examiner alleges that Chabaud discloses that IL-17 levels are elevated in the synovium supernatant of RA patients and that "RA synovium T cells that are producing IL-17 can activate mesenchymal cells leading to an increased proinflammatory pattern" and that anti-IL-17 antibody can reduce production of IL-6 and LIF (which are alleged inflammatory mediators), present at high concentration in RA synovial fluid and involved in the pathogenesis of RA, as taught by Carroll. The Examiner further suggest that the "control of the production and action of IL-17 may represent a therapeutic target for reducing the enhancing effect of monocyte-derived cytokines."

While the Examiner acknowledges that neither Chabaud nor Carroll teach a method of using an IL-17 antagonist *in vivo* to treat a cartilagenous disorder, such as RA, the Examiner alleges one of ordinary skill in the art would be motivated to try in light of Chabaud's teaching that anti-IL-17 antibody significantly reduces the pro-inflammatory cytokines IL-6 and LIF.

Finally, the Examiner alleges that the "preventing features" recited in Claims 21-26, 28-29 and 33-34 would be an inherent property of the IL-17 antibody.

In response, Applicants respectfully submit that Chabaud *et al.* does disclose that IL-17 increases the production of the cytokines IL-6 and LIF. That is, any activity which might be possessed by IL-17 is due solely to the ability of this cytokine to increase the production of IL-6 and/or LIF. However, contrary to the Examiner's suggestion, Chabaud does not teach the use of anti-IL-17 antibodies. Moreover, Chabaud *et al.* discloses in col. 2 on page 412 that cultures of osteoarthritic synovium "did not contain . . . IL-17-related activity." In this way, the clear implication is that Chabaud *et al.* teaches away from using IL-17 antagonists for the treatment of osteoarthritis. In fact, Chabaud *et al.*, is very clear in not making any statements about any therapeutic potential for disease states; it only indicates that "control of the production and action of IL-17 may represent a therapeutic target for reducing the enhancing effect of monocyte-derived cytokines." (page 413). However, there is no suggestion that, such "monocyte-derived cytokines" might be responsible for IL-17 mediated inflammatory disorders.

Carroll *et al.* does report that others have observed therapeutic effect in RA patients treated with anti-IL-6 antibody. However, the experimental data in Carroll *et al.* is exclusively directed to the effect of LIF on cartilage and to the correlation between LIF and rheumatoid arthritic joints. There is absolutely no mention of IL-17 or its effect on IL-17 mediated inflammatory disorders.

Applicants have shown a direct-causative effect of IL-17 on cartilage catabolism. Applicants have further demonstrated that the direct administration of anti-IL-17 antibodies mitigates IL-17-mediated destruction. This is significant because it has been demonstrated that mitigation of IL-17 and not mitigation of another cytokine potentially related to IL-17 is shown to have therapeutic effect. At best, the Examiner's combination of Chabaud *et al.* and Carroll *et al.* might suggest a therapy based on the administration of anti-IL-6 antibodies. However, nothing in either Chabaud *et al.*, or Carroll *et al.*, suggests that the administration of anti-IL-17

antibodies might be effective for the treatment of both rheumatoid arthritis, osteoarthritis and IL-17 mediated inflammatory disorders. To the contrary, the statements in Chabaud *et al.* that the effect of IL-17 is different on rheumatoid v. osteoarthritic tissues. Thus, the combined disclosure of Chabaud *et al.* and Carroll *et al.* fails to recognize and does not appreciate that a common cytokine can be effective at treating cartilage damaged by both rheumatoid arthritis and osteoarthritis. Thus, the problem solved by the invention is distinctly different from that suggested by the Examiner's combination of the prior art.

Next, the amendment and/or cancellation of the alleged "preventing features" of Claims 21-26, 28, 29, 33 and 34 has rendered application of this aspect of the rejection to these claims moot.

Applicants respectfully request reconsideration and withdrawal of the rejection of Claims 1-9, 21-26, 28-29 and 37-40 under 35 U.S.C. § 103 (Claims 13-14, 33-34 having been cancelled).

***The Second Rejection under 35 U.S.C. § 103***

Claims 1-4, 8-9, 13-14, 21-26, 28-29, 33-34 and 37-39 stand rejected under 35 U.S.C. § 103, as allegedly being unpatentable over Kotake *et al.*, *J. Clin. Invest.* 103:1345-1352 (1999), and Chabaud *et al.*, *Arthritis and Rheumatism* 42: 963-970 (1999) in view of Carroll *et al.*, *supra*.

The Examiner alleges that Kotake discloses that the concentration of IL-17 in the synovial fluids and tissues is elevated in RA patients, but not in OA or trauma patients, that IL-17 is a crucial cytokine for osteoclastic resorption in RA patients, and that anti-IL-17 antibody significantly inhibited osteoclast formation induced by culture media of RA synovial tissues. The Examiner further alleges that Chabaud *et al.* discloses that anti-IL-17 antibody reduces production of IL-6, a proinflammatory cytokine, present at high concentrations in RA synovial fluid and involved in the pathogenesis of RA, as taught by Carroll.

The Examiner asserts that it would have been obvious to a person of ordinary skill in the art at the time the invention was made to treat a patient with RA (a cartilagenous disorder or a degenerative cartilagenous disorder of articular cartilage) by administering an effective amount of an antagonist to IL-17. The Examiner further asserts that one of ordinary skill would have

been motivated to practice the claimed method because of Chabaud's teaching that anti-IL-17 antibody significantly reduces the production of the pro-inflammatory cytokines IL-6 and LIF.

The Examiner further asserts that the "preventing features" recited in Claims 21-26, 28-29 and 33-34 would be an inherent property of the IL-17 antibody.

In response, Applicants respectfully submit that Chabaud *et al.* and Carroll *et al.* are discussed above. Continuing, Applicants respectfully confirm that Kotake *et al.*, does disclose that anti-IL-17 antibody causes inhibition of osteoclast formation induced by culture media from RA synovial tissues. However, nothing in Kotake *et al.* describes any effect whatsoever on anti-IL-17 antibody on cartilage catabolism, much less on IL-17 mediated inflammatory disorders. As a result, there is simply no suggestion or motivation either individually or combined in Chabaud *et al.*, Carroll *et al.* or Kotake *et al.* of the use of IL-17 antibodies to treat IL-17 mediated inflammatory disorders.

It is important to emphasize that none of the references of the rejection teaches that the anti-IL-17 antibody has a direct therapeutic effect on cartilage. That is, the cited prior art does not teach that IL-17 antibody can and does mitigate the deleterious effects of IL-17. As articulated in the rebuttal to the previous rejection, the prior art combination does not appreciate that a common cytokine (*i.e.*, IL-17) can mediate cartilage damaged from both osteo- and rheumatoid arthritis as well as other IL-17 mediated inflammatory disorders.

It is further clear that none of the references cited by the Examiner under any of the rejections under 35 U.S.C. § 103 correlate IL-17 with cartilage damaged due to osteoarthritis. While IL-17 is alleged to induce production of IL-6 and LIF, cytokines with known destructive effects on cartilage, the absence of any indication in the prior art that IL-17 might also be responsible for osteoarthritic damage is suggestive that the mechanism of action of IL-17 is distinctly different than that of IL-6. Thus, the destructive effect of IL-17 on cartilage is not due merely to its ability to induce secretion of IL-6 or of other known cytokines with catabolic effect on cartilage. As a result, one of ordinary skill would not have appreciated that a single cytokine (*i.e.*, IL-17) would be effective in treating cartilage damaged from rheumatoid and osteo-arthritis as well as other IL-17 mediated inflammatory disorders.

Next, amendment and/or cancellation of the "preventing features" of Claims 21-26, 28-29 and 33-34 renders application of this particular aspect of the rejection to these claims moot.

Applicants respectfully request reconsideration and withdrawal of the rejection of Claims 1-4, 8-9, 21-26, 28-29 and 37-39 under 35 U.S.C. § 103 (Claims 13-14, 33-34 having been cancelled).

***The Third Rejection under 35 U.S.C. § 103***

Claims 15-16, 18, 35-36 stand rejected under 35 U.S.C. § 103(a), as allegedly being unpatentable over Chabaud *et al.* and Arend *et al.*, *Annu. Rev. Immunol.* 16: 27-55 (1998).

The Examiner's characterizations of Chabaud are recited above. Moreover, the Examiner also asserts that Chabaud teaches that IL-17 can envoke an enhanced pro-inflammatory secretion profile when combined with IL-1 (Figures 3-4).

The Examiner alleges that Arend *et al.* teaches a method of treating patients with rheumatoid arthritis with IL-1Ra, and indicates improvement of these patients in clinical parameters and in radiographic evidence of joint damage.

The Examiner further acknowledged that neither reference teaches a combined therapy of an IL-17 antagonist and IL-1Ra to treat a cartilagenous disorder. However, the Examiner argues that it would have been obvious at the time the invention was made to treat a patient with RA by combining the IL-17 antagonist and at least one cartilage agent, such as IL-1Ra, based upon the indications of Chabaud (synergistic effects of IL-17 and IL-1), and the positive results taught by Chabaud and Arend (IL-17 and IL-1Ra). Finally, the Examiner argues that one of ordinary skill would have been motivated to practice a combined therapy, with a reasonable expectation of success because of the potential for additive or synergetic effects of a combination of two compound classes that are known individually to have therapeutic effect on rheumatoid arthritis.

Finally, the Examiner asserts that the "preventing features" recited in Claims 35 and 36 would be an inherent property of the IL-17 antibody and IL-1Ra.

In response, Applicants respectfully submit the cancellation of Claims 15-16, 18, 35-36 renders the rejection moot.

Attached hereto is a marked-up version of the changes made to the specification and claims by the current amendment. The attached page is captioned **"Version with markings to show changes made."**

Applicants believe that this application is now in condition for immediate allowance and respectfully request that the outstanding objections and rejections be withdrawn and this case passed to issue.

The Examiner is invited to contact the undersigned at (650) 225-1489 in order to expedite the resolution of any remaining issues.

Respectfully submitted,
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## VERSION WITH MARKINGS TO SHOW CHANGES MADE

**In the specification:**

The title has been amended as follows:

USE OF ANTI-IL-17 ~~AND LIF ANTAGONISTS~~ ANTIBODIES FOR THE TREATMENT OF CARTILAGENOUS DISORDERS

The paragraph at page 4, lines 1-12 has been amended as follows:

IL-17 has been shown to be produced by primary peripheral blood CD4+ T-cells upon stimulation, but was not detected in unstimulated peripheral blood T-cells, peripheral blood cells, and EBV-transformed B-cell line, or a T-cell leukemia line. WO 00/20593. IL-17 is expressed in arthritic, but not normal joints (reviewed in Martel-Pelletier, J. *et al.*, *Front. Biosci.* 4: d694-703 (1999). While expression of IL-17 is restricted, the IL-17 receptor is widely expressed, a property consistent with the pleiotropic activities of IL-17. IL-17 stimulates epithelial, endothelial, and fibroblastic cells to secrete cytokines such as IL-6, IL-8, and granulocyte-colony-stimulating factor (G-CSF), as well as prostaglandin $E_2$ ($PGE_2$). Spriggs, M.K., *supra.*; Broxmeyer, H.E., *supra.* IL-17 can sustain proliferation and preferential maturation of CD34-hemopoietic progenitors into neutrophils when cultured with fibroblasts. As such, production of IL-17 may be the key mechanism by which T-cells regulate the hematopoietic system. See, Yao, *et al.*, *J. Immunol.*, 155(12): 5483-5486 (1995) [Yao-2], Fossiez, *et al.*, *J. Exp. Med.*, 183(6): 2593-2603 (1996); Kennedy, *et al.*, *J. Interferon Cytokine Res.*, 16(8): 611-617 (1996).

The paragraph at page 16, lines 21-27 has been amended as follows:

IGF-1 has been proposed for the treatment or prevention of osteoarthritis. In fact, intra-articular administration of IGF-1 in combination with sodium pentosan polysulfate (a chondrocyte catabolic activity inhibitor) caused improved histological appearance, and near-normal levels of degradative enzymes (neutral metalloproteinases and collagenase), tissue inhibitors of metalloproteinase and matrix collagen. R.A. Rogachefsky, *et al.*, *Ann. N.Y. Acad. Sci.* 732: ~~889-95~~392-394 (1994). The use of IGF-1 either alone or as an adjuvant with other growth factors to stimulate cartilage regeneration has been described in WO 91/19510, WO 92/13565, US 5,444,047, EP 434,652.

The paragraph at page 17, lines 11-24 has been amended as follows:

Cartilage matrix degradation is believed to be due to cleavage of matrix molecules (proteoglycans and collagens) by proteases (reviewed in Woessner JF Jr., "Proteases of the extracellular matrix", in Mow, V., Ratcliffe, A. (eds): Structure and Function of Articular Cartilage. Boca Raton, FL, CRC Press, 1994 and Smith R.L., *Front. In Biosci.* 4:d704-712 (1999). While the key enzymes involved in matrix breakdown have not yet been clearly identified, matrix metalloproteinases (MMPs) and "aggrecanases" appear to play key roles in joint destruction. In addition, members of the serine and cysteine family of proteinases, for example the cathepsins and urokinase or tissue plasminogen activator (uPA and tPA) may also be involved. Plasmin, urokinase plasminogen activator (uPA) and tissue plasminogen activator (tPA) may play an important role in the activation pathway of the metalloproteinases. Evidence connects the closely related group of cathepsin B, L and S to matrix breakdown, and these cathepsins are somewhat increased in OA. Many cytokines, including IL-1, TNF-a and LIF induce MMP expression in chondrocytes. Induction of MMPs can be antagonized by TGF-β and is potentiated, at least in rabbits, by FGF and PDGF. As shown by animal studies, inhibitors of these proteases (MMPs and aggrecanases) may at least partially protect joint tissue from damage *in vivo*.

The paragraph at page 19, lines 28-33 has been amended as follows:

The pathology of OA involves not only the degeneration of articular cartilage leading to eburnation of bone, but also extensive remodelling of subchondral bone resulting in the so-called sclerosis of this tissue. These bony changes are often accompanied by the formation of subchondral cysts as a result of focal resorption. Agents which inhibit bone resorption, *i.e.* osteoprotegerin or bisphosphonates have shown promising results in animal models of arthritis, and therefore show promise in treating cartilagenous disorders. Kong *et al. Nature* 402: 304-308 (1999).

The paragraph at page 32, lines 6-15 has been amended as follows:

B. Mouse Patellae Assay

This experiment examines the effects of the test compound on proteoglycan synthesis in the patellae (knee caps) of mice. This assay uses intact cartilage (including the underlying bone) and thus tests factors under conditions which approximate the *in vivo* environment of cartilage. Compounds are either added to patellae *in vitro*, or are injected into knee joints *in vivo* prior to analysis of proteoglycan synthesis in patellae *ex vivo*. As has been shown previously, *in vivo* treated patellae show distinct changes in PG synthesis *ex vivo*. (Van den Berg *et al.*, *Rheum. Int.* 1: 165-9 (1982); ~~Vershure~~Verschure, P.J. *et al.*, *Ann. Rheum. Dis.* 53: 455-460 (1994); and Van de Loo *et al.*, *Arthrit. Rheum.* 38: 164-172 (1995). In this model, the contralateral joint of each animal can be used as a control. The procedure is described in greater detail in the examples.

The paragraph beginning at page 32, lines 30 and ending at page 33, line 6 has been amended as follows:

D. Aggrecanase assay

Aggrecan is the major proteoglycan of cartilage and largely responsible for the mechanical properties of articular cartilage. Arner *et al.*, *J. Biol. Chem.* 274(10):6594-6601 (1999). Aggrecan contains two N-terminal globular domain, G1 and G2, separated by a proteolytically sensitive interglobular domain (IGD), followed by a glycosaminoglycan (GAG) attachment region and a C-terminal globular domain (G3). The G1 domain of aggrecan interacts with hyaluronic acid and link protein to form large aggregates containing multiple aggrecan monomers that are trapped within the cartilage matrix. Hardingham, T.E. & Muir, H., *Biochim. Biophys. Acta* 279: 401-405 (1972); Heinegard, D. & Hascall, V.C., *J. Biol. Chem.* 249: 4250-4256 (1974); Hardingham, T.E., ~~*Biochem*~~*Biochem. J.* 177: 237-247 (1979). Aggrecan provides normal cartilage with its properties of compressibility and resilience, and is one of the first matrix components to undergo measurable loss in arthritis. This loss appears to be due to an increased rate of aggrecan degradation that can be attributed to proteolytic cleaveage within the IGD of the core protein. Cleavage within this region generates large C-terminal, GAG-containing aggrecan fragments lacking the $G_1$ domain which are unable to bind to hyaluronic acid and thus diffuse out of the cartilage matrix.

The paragraph at page 33, lines 7-14 has been amended as follows:

Cleavage of aggrecan has been shown to occur at $Asn^{341}$-$Phe^{342}$ and at $Glu^{373}$-$Ala^{374}$ within the interglobular domain. Matrix mellaoproteinases (MMP-1, -2, -3, -7, -8, -9 and -13) are known to cleave aggrecan *in vitro* at the $Asn^{341}$-$Phe^{342}$ site. Fosang *et al.*, *J. Biol. Chem.* 266: 15579-15582 (1991); Flannery, C.R. *et al.*, *J. Biol. Chem.* 267: 1008-1014 (1992); Fosang *et al.*, *Biochem. J.* 295: 273-276 (1993); Fosang *et al.*, *J. Biol. Chem.* 267: 19470-19474 (1992); Fosang *et al.*, *FEBS Lett.* 380: 17-20 (1996). Identification of G1 fragments formed by cleavage at the $Asn^{341}$-$Phe^{342}$ site within human articular cartilage as well as in synovial fluids suggests a role for MMPs in proteoglycan degredation *in vivo*. Arner *et al.*, *supra*. However, these MMPs were not responsible for the cleavage at the $Glu^{373}$-$Ala^{374}$ site.

The paragraph at page 63, lines 8-17 has been amended as follows:

**Example 1A**

**Effect of IL-17 upon cartilage matrix metabolism**

To determine whether IL-17 affects cartilage matrix metabolism, porcine articular cartilage explants were treated with a range of IL-17 concentrations, and proteoglycan synthesis and breakdown were measured. At concentrations as low as 0.1 ng/ml, IL-17 induced significant cartilage breakdown (Fig. 1A) and inhibited new matrix synthesis (Figure 1B), with comparable potency to IL-1α. When IL-1α (1 ng/ml) and IL-17 (0.1 or 1 ng/ml) were combined, an enhancing, apparently additive, effect was observed on both matrix breakdown (Fig. 1C) and synthesis (Fig. 1D). Unlike what was found in a prior study (Chabaud *et al.*, *Arthritis Rheum.* ~~36: 790-94 (1998)~~42(5): 963-970 (1999), no synergism between IL-1α and IL-17 was observed.

The paragraph at page 67, lines 1-12 has been amended as follows:

**Example 3**

***In vivo* effects of IL-17**

The patellar assay determines the *in vitro* and *in vivo* effect of the tested compound on proteoglycan synthesis in the patellae of mice. The patella is a very useful model to study the effects of the test compound because it permits the evaluation on cartilage which has not been removed from the underlying bone. Moreover, since each animal has one patellae in each leg, experiments can be performed using the contralateral joint as a control. This assay involves injection of a protein into the intra-articular space of a (mouse) knee joint, and subsequent

harvest (within a few days after injection) of the patella (knee cap) for measurement of matrix synthesis. The procedure performed herein, has been previously used to measure effects of cytokines *in vitro* and *in vivo* (Van den Berg *et al.*, *Rheum. Int.* 1: 165-9 (1982); ~~Vershure~~Verschure P.J. *et al.*, *Ann. Rheum. Dis.* 53: 455-460 (1994); and Van de Loo *et al.*, *Arthrit. Rheum.* 38: 164-172 (1995)).

The paragraph at page 70, lines 11-25 has been amended as follows:

Soluble factors made by T cells, monocytes and synovial fibroblasts may act in concert as these cell types are found in close proximity in RA synovium. The fact that IL-17 induces expression of other cytokines, such as TNF-α and IL-1α Chabaud *et al.*, *J. Immunol.* 161: 409-414, (1998); Jovanovic *et al.*, *J. Immunol.* 160: 3513-21 (1998), which are found at high levels in diseased joints, Arend and Dayer, *Arthritis Rheum.* 38: 151-60 (1995), raises the intriguing possibility that IL-17 is involved in the initiation of the inflammatory cascade in arthritis. Overproduction of IL-17 by human mononuclear cells is triggered by IL-1β and IL-15 (Ziolkowska *et al.*, *supra*), and IL-17 is likely responsible for production of IL-6 (Chaubaud *et al.*, *supra*) and LIF, Chabaud *et al. J. Immunol.* 161: 409-414 (1998) and induction of bone resorption (Kotake *et al.*, *J. Clin. Invest.* 103: 1345-1351 (~~2000~~1999) by RA synovial tissues. Thus, IL-17 may be one of the primary catabolic cytokines in arthritis. IL-17 may also perpetuate the cycle of cytokine synthesis as overproduction of IL-17 by human mononuclear cells is triggered by IL-1β and IL-15 (Ziolkowska *et al.*, *supra*). As described herein, IL-17 disrupted cartilage matrix homeostasis and augmented the detrimental effects of IL-1α on articular cartilage matrix turnover and nitric oxide production. Thus, the presence of IL-17 in a diseased joint can amplify the inflammatory cascade and exacerbate skeletal tissue breakdown in human joints.

The paragraph at page 78, lines 21-33 has been amended as follows:

Articular cartilage explants: The metacarpophalangeal joint of a 4-6 month old female pigs was aseptically dissected, and articular cartilage is removed by free-hand slicing in a careful manner so as to avoid the underlying bone. The cartilage was minced and cultured in bulk for at least 24 hours in a humidified atmosphere of 95% air 5% $CO_2$ in serum free (SF) media (DMEM/F12, 1:1) with 0.1% BSA and antibiotics. After washing three times, approximately 80 mg of

articular cartilage was aliquoted into micronics tubes and incubated for at least 24 hours in the above SF media. Test proteins were then added at 1% either alone or in combination with IL-1α (10 ng/ml). Media was harvested and changed at various timepoints (0, 24, 48, 72 hours) and assayed for proteoglycan content using the 1,9-dimethyl-methylene blue (DMB) colorimetric assay described in Farndale and Buttle, *Biochem. Biophys. Acta* ~~993~~883: 173-177 (~~1985~~1986). After labeling (overnight) with $^{35}$S-sulfur, the tubes were weighed to determine the amount of tissue. Following an overnight digestion, the amount of proteoglycan remaining in the tissue as well as proteolgycan synthesis ($^{35}$S-incorporation) was determined.

**In the claims:**

Claims 45-46 have been added.

Claim 2, 10-18, 22, 30-36 and 38 have been cancelled.

Claims 1, 9, 21, 29 and 37 have been amended as follows:

1. A method of treating ~~cartilage damaged from a cartilagenous~~an IL-17 mediated, inflammatory cartilagenous disorder comprising contacting the cartilage with an effective amount of ~~an antagonist to~~ anti-IL-17 ~~or LIF~~ antibody.

9. The method of Claim 8, wherein the antagonist to IL-17 ~~or LIF~~ is administered by direct injection into an afflicted cartilagenous region or joint.

21. A method of ~~preventing~~reducing further cartilage damage~~d~~ caused by a cartilagenous disorder comprising contacting the cartilage with an effective amount of an anti-IL-17 ~~or LIF antagonist~~antibody.

29. The method of Claim 28, wherein the IL-17 ~~and LIF~~ antagonist is administered by direct injection into an afflicted cartilagenous region or joint.

37. A method of treating a mammal suffering from ~~a~~an IL-17 mediated, inflammatory cartilagenous disorder, comprising administering to said mammal a therapeutically effective amount of an ~~antagonist to~~ anti-IL-17 ~~or LIF~~ antibody.